

DETAILED ACTION

Status of Claims

Claims 1, 2 and 5-25 are pending and are thus examined herein on the merits for patentability. No claim is allowed at this time.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
 2. Ascertaining the differences between the prior art and the claims at issue.
 3. Resolving the level of ordinary skill in the pertinent art.
 4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
1. Claims 1, 2, 5-14 and 16-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,713,376 (hereinafter *Berger '376*) in view of *Musser et al.*, *Nature*, 11 April 2002, 416, 599-600 (hereinafter *Musser et al.*).

Applicant claims:

Applicants claim a method of reducing the nicotine content of a tobacco plant through applying glucose oxidase to said plant in an amount effective inhibit the synthesis of nicotine such that upon use non-addictive levels in the CNS blood plasma of the user are achieved.

Applicants also claim a tobacco plant as well as tobacco plant leaves, which have been treated with glucose oxidase in an amount effective inhibit the synthesis of nicotine such that upon use non-addictive levels in the CNS blood plasma of the user are achieved, wherein the tobacco plant leaves are selected from *Nicotiana tabacum*, *Nicotiana rustica* and *Nicotiana glutinosa*.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Berger '376 teaches a desire to produce a tobacco product with decreased levels of nicotine to an extent that upon use non-addictive levels in the CNS blood plasma of the user are achieved (column 2, lines 35-38 and 51-59).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Berger '376 does not teach applying glucose oxidase to the tobacco plant. However, Musser et al. teach the saliva of the caterpillar *Helicoverpa zea* can reduce the amount of toxic nicotine released by the tobacco plant *Nicotiana tabacum* (page 599, first paragraph). Musser et al. further teach feeding by caterpillars with intact

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spinnerets, the principal secretory structures of the labial salivary glands of *Helicoverpa zea*, reduced foliar nicotine levels by over 26% compared with the control (page 599, middle column, lines 6-10). Musser et al. also teach treatment of individual leaves with one of four preparations: active purified glucose oxidase, unpurified salivary-gland extract, inactivated (autoclaved) purified glucose oxidase, or water, wherein leaves treated with salivary extract received 20 micrograms glucose oxidase in total (page 599, third column, lines 16-22). Musser et al. also teach each wound on the plant received 10 microliters of water (page 599, third column, lines 22-23), which according to the specification would be a suitable carrier (page 11, lines 21-22).

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one skilled in the art at the time of the invention to reduce the amount of nicotine in *Nicotiana tabacum* to a non-addictive level, as taught by Berger '376, through applying glucose oxidase from *Helicoverpa zea*, or a biochemical source, as reasonably taught by Musser et al. The concentration of glucose oxidase or the necessary number of treatments to achieve non-addictive levels is well within the purview of a person skilled in the art at the time of the instant invention. A person skilled in the art would be motivated to determine the appropriate concentration or number of treatments of glucose oxidase required to achieve non-addictive levels in order produce a cigarette product that is non-addictive, as reasonably taught by Berger '376, which would inherently yield the tobacco plant and tobacco plant leaves containing non-addictive levels of nicotine.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicants arguments filed 27 August 2007 have been fully considered, but are not found persuasive. Applicants argue on pages 3-5 that Berger '376 teaches treating nicotine existing in the tobacco plant with a chemical substance to convert the nicotine into neutral or beneficial compounds, whereas Musser et al. teach reducing the amount of harmful nicotine released by the tobacco plant by counteracting the production of nicotine induced by the caterpillar feeding on the plant, which is not converting nicotine to a harmless byproduct, but instead inhibits the production of nicotine. Therefore, Applicants argue that Berger '376 does not provide any guidance to one of ordinary skill in the art to modify what is fairly taught in Musser et al.

However, the examiner respectfully disagrees. Both Berger '376 and Musser et al. are drawn to the same problem to be solved: reducing the levels of nicotine in a tobacco plant. Therefore, motivation is drawn from the nature of the problem to be solved, reducing nicotine levels in tobacco plants.

Applicants argue on pages 10-12 of their Remarks filed 8 March 2007 that the behavior of complex biological systems such as tobacco plant is unpredictable, and thus

there would be no reasonable expectation of success to reduce the nicotine content of tobacco plants to non-addictive levels by simply employing concentrated solutions and/or multiple treatments of glucose oxidase. Applicants further rely on the teachings of a Gorder article and a Marino slide presentation, submitted in conjunction with their Remarks.

However, the examiner respectfully disagrees. Musser et al. clearly provides a reasonable expectation of success in using glucose oxidase from *Helicoverpa zea* to reduce nicotine levels in tobacco plants. Musser et al. teach that glucose oxidase converts D-glucose and molecular oxygen to D-gluconic acid and hydrogen peroxide (pg. 599, 3rd column, ll. 4-7), and that both H₂O₂ and D-gluconic acid individually at 40 mM concentrations reduced nicotine levels in tobacco plant leaves by 43.6% and 29.3%, respectively (pg. 599, 3rd column, ll. 36-43). Therefore, one of ordinary skill in the art would expect that higher concentrations or repeated applications of glucose oxidase would lead to an increase in the inhibition of nicotine production. "A person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product [was] not of innovation but of ordinary skill and common sense." See MPEP 2143(E).

Also, the Gorder article states that researchers can determine whether a reaction is predictable, or whether it might be what they call "quirky", i.e. prone to switching behavior that *occasionally* produces strange results. Therefore, the Gorder article recognizes that only *occasionally* do the biological reactions produce strange results. The Marino slides (slide 7) state that when we alter specific components of complex

biological systems the results are unpredictable. Marino further provides the example that directly adding twice the value of an enzyme would not result in twice the "output" of the cell (i.e. the resultant production of the cell is nonlinear). However, Marino does not state that adding twice the enzyme does not result in any increase of output of the cell, but merely that the output will not be exactly twice the original output. Marino even states on slide 6 that essentially every natural system is nonlinear, even though many natural systems can be satisfactorily approximated as linear systems. Therefore, Marino acknowledges that many systems will behave in a satisfactorily predictable manner.

Also, it is well-known in the art that application of increased concentrations of drugs results in increased effect in biological systems. That is why all drugs have minimum inhibitory concentrations (MIC), half maximal (median) inhibitory concentrations (IC_{50}), median effective concentrations (EC_{50}), and median lethal concentrations (LD_{50}). It is well-known in the art that any concentration of drug above the MIC, IC_{50} , EC_{50} , or LD_{50} value is expected to have an increased effect compared to concentrations below the MIC, IC_{50} , EC_{50} , or LD_{50} value, respectively. Thus, one of ordinary skill in the art would expect that addition of a higher concentration of glucose oxidase, or sequential applications would result in an increase in the inhibition of nicotine production in the tobacco plant. Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to try increased concentrations or sequential applications of glucose oxidase in an attempt to obtain non-additive levels of nicotine in tobacco plants.

2. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Berger '376 and Musser et al., as applied to Claims 1, 2, 5-14 and 16-20 above, further in view of Hibi et al., The Plant Cell, 1994, 6, 723-735 (hereinafter Hibi et al.).

Applicant claims:

The Applicant claims a method of reducing the nicotine content of a tobacco plant through applying glucose oxidase to said plant in an amount effective inhibit the synthesis of nicotine such that upon use non-addictive levels in the CNS blood plasma of the user are achieved, wherein the tobacco plant is a genetically modified plant exhibiting reduced levels of nicotine as compared to non-genetically modified tobacco plants.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Berger '376 teaches a desire to produce a tobacco product with non-addictive levels of nicotine, as discussed above. Musser et al. teach glucose oxidase from *Helicoverpa zea* reduces nicotine levels in tobacco plants, as discussed above.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Neither Berger'376 nor Musser et al. teach reducing the level of nicotine in a genetically modified tobacco plant that exhibits reduced nicotine levels as compared to a non-genetically modified tobacco plant. However, genetic engineering of tobacco plants for the purpose of reducing nicotine levels is known in the art, and such methods

have reduced nicotine in tobacco (specification, paragraph bridging pages 1 and 2). Also, Hibi et al. teach genetically modified tobacco plants (i.e. *nic1* and *nic2* mutations), which reduce levels of nicotine in said plants (abstract and page 733, 1st column, lines 8-10).

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one skilled in the art at the time of the invention to apply glucose oxidase, as reasonably suggested by Musser et al., to genetically modified tobacco plants which already have reduced levels of nicotine, in order to obtain a tobacco product with non-addictive levels of nicotine. One of ordinary skill in the art would have been motivated to start with genetically modified tobacco plants which have reduced levels of nicotine as compared to non-genetically modified tobacco plants because the concentration or number of treatments of glucose oxidase would be less than required for non-genetically modified tobacco plants in order to achieve non-addictive levels of nicotine.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicants argue on pages 5-7 that Hibi et al. does not teach a method of reducing nicotine in tobacco plants, thus it would not be obvious to add glucose oxidase to genetically engineered tobacco plants.

However, the examiner respectfully disagrees. Hibi et al. clearly teach that low nicotine content Cuban cigar varieties were incorporated into cigarette varieties through a series of backcrosses to meet the expected demand for low-nicotine cigarettes, and LA Burley 21 was thus developed as a genetically stable breeding line with a very low-alkaloid content (pg. 723, left column, last paragraph). Therefore, Hibi et al. clearly teach motivation for using genetically modified tobacco plants to obtain a low-nicotine cigarette. Thus, it would have been obvious to use the genetically modified tobacco plants, as taught by Hibi et al., that already have low levels of nicotine, and further treat said tobacco plants with glucose oxidase to lower the nicotine to non-addictive levels, as reasonably suggested by the combined teachings of Musser et al. and Berger '376.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is 571-272-9924. The examiner can normally be reached on 8:30 AM to 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Johann R. Richter/

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Supervisory Patent Examiner, Art Unit 1616